Zalcitabine

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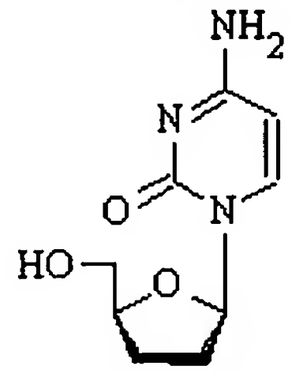
Zalcitabine (2'-3'-dideoxycytidine, **ddC**), also called dideoxycytidine, is a nucleoside analog reverse transcriptase inhibitor (NARTI) sold under the trade name Hivid®.

The recommended dosage is 0.750 mg (one tablet) every 8 hours, as part of a combination regimen.

Zalcitabine appears less potent than some other nucleoside RTIs, has an inconvenient three-times daily frequency and is associated with serious adverse events. For these reasons it is now rarely used to treat human immunodeficiency virus (HIV).

Contents



Zalcitabine

Systematic (IUPAC) name

4-amino-1-[5-(hydroxymethyl) tetrahydrofuran-2-yl]- 1H-pyrimidin-2-one

Identifiers

CAS number	7481-89-2 (http://www.nlm.nih.gov/cgi/mesh/2006/MB_cgi?term=7481-89-2&rn=1)
ATC code	J05AF03 (http://www.whocc.no/atcddd/indexdatabase/index.php?query=J05AF03)
PubChem	24066 (http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=24066)
DrugBank	APRD00562 (http://redpoll.pharmacy.ualberta.ca/drugbank/cgi-bin/getCard.cgi?CARD=APRD00562)

Chemical data

Formula	$C_9H_{13}N_3O_3$
Mol. weight	211.218 g/mol

Pharmacokinetic data

Bioavailability	>80%
Protein binding	<4%
Metabolism	Hepatic
Half life	2 hours
Excretion	Renal (circa 80%)

Therapeutic considerations

Pregnancy cat.	D(AU) C(US)
Legal status	POM(UK) Rx-only(US)
Routes	Oral

History

Zalcitabine was developed in the National Cancer Institute (NCI) by Samuel Broder, Hiroaki Mitsuya, and Robert Yarchoan at the National Cancer Institute (NCI). Like didanosine, it was then licensed because the NCI may not market drugs. The National Institutes of Health (HIH) thus licensed it to Hoffman LaRoche.

Zalcitabine was the third antiretroviral to be approved by the Food and Drug Administration (FDA) for the treatment of HIV infection and AIDS. It was approved on Jun 19, 1992 as a monotherapy and again in 1996 for use in combination with Zidovudine (AZT). Using combinations of NRTIs was in practice prior to the second FDA approval and the triple drug combinations with dual NRTIs and a protease inhibitor (PI) were not far off by

this time.

Mechanism of action

Zalcitabine is an analog of pyrimidine. It is a derivative of the naturally existing deoxycytidine, made by replacing the hydroxyl group in position 3' with a hydrogen.

It is phosphorylated in T cells and other HIV target cells into its active triphosphate form, ddCTP. This active metabolite works as a substrate for HIV reverse transcriptase, and also by incorporation into the viral DNA, hence terminating the chain elongation due to the missing hydroxyl group. Since zalcitabine is a reverse transcriptase inhibitor it possess activity only against retroviruses.

Pharmacokinetics

Zalcitabine has a very high oral absorption rate of over 80%. It is predominantly eliminated by the renal route, with a half-life of 2 hours.[1]

Drug interactions

Lamivudine (3TC) significantly inhibits the intracellular phosphorylation of zalcitabine to the active form, and accordingly the drugs should not be administered together.[1]

Additionally, zalcitabine should not be used with other drugs that can cause peripheral neuropathy, such as didanosine and stavudine.[1]

Adverse events

The most common adverse events at the beginning of treatment are nausea and headache. More serious adverse events are peripheral neuropathy, which can occur in up to 33% of patients with advanced disease, oral ulcers, oesophageal ulcers and, rarely, pancreatitis.[1]

Resistance

Resistance to zalcitabine develops infrequently compared with other nRTIs, and generally only occurs at a low level.[2] The most common mutation observed *in vivo* is T69D, which does not appear to give rise to cross-resistance to other nRTIs; mutations at positions 65, 74, 75, 184 and 215 in the *pol* gene are observed more rarely. [1][2]

Sources

1. ^ *a b c d e* HIVID® (zalcitabine) tablets. Product information. (September 2002) (http://www.rocheusa.com/products/hivid/pi.pdf)
2. ^ *a b* Moyle GJ. Use of viral resistance patterns to antiretroviral drugs in optimising selection of drug combinations and sequences. *Drugs* 1996;52:168-185

Further reading

- Yarchoan R, Mitsuya H, Broder S. AIDS therapies. *Scientific American* 1988;259(4):110-9.
- Harvey Stewart C. in *Remington's Pharmaceutical Sciences* 18th edition: (ed. Gennard, Alfonso R.) Mack Publishing Company, 1990
- Rang H.P., Dale M.M., Ritter J.M.: *Pharmacology*, 3rd edition. Pearson Professional Ltd, 1995.
- Mitsuya H, Broder S. Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotropic virus type III/lymphadenopathy virus-associated virus (HTLV-III/LAV) by 2',3'-dideoxynucleosides. *Proc Natl Acad Sci USA* 1986;83:1911-5.
- Yarchoan R, Perno CF, Thomas RV, *et al.* Phase I studies of 2',3'-dideoxycytidine in severe human immunodeficiency virus infection as a single agent and alternating with zidovudine (AZT). *Lancet* 1988;1:76-81.
- Mitsuya H, Yarchoan R, Broder S. Molecular targets for AIDS therapy. *Science* 1990;249:1533-44.
- NIH Bio and Oral History of Samuel Broder describing the development of anti-HIV drugs: http://aidshistory.nih.gov/transcripts/bios/Samuel_Broder.html
- NIH Bio and Oral History of Robert Yarchoan describing the development of anti-HIV drugs: http://aidshistory.nih.gov/transcripts/bios/Robert_Yarchoan.html
- Moyle G. A re-evaluation of zalcitabine. *Expert Opin Investig Drugs* 1998;7:451-62

Antivirals (primarily J05A, also S01AD and D06BB)		
Anti-herpesvirus agents		Aciclovir, Cidofovir, Docosanol, Famciclovir, Fomivirsen, Foscarnet, Ganciclovir, Idoxuridine, Penciclovir, Trifluridine, Tromantadine, Valaciclovir, Valganciclovir, Vidarabine
Anti-influenza agents		Amantadine, Oseltamivir, Peramivir, Rimantadine, Zanamivir
Antiretroviral drugs	**NRTIs**	Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, **Zalcitabine**, Zidovudine
	NtRTIs	Tenofovir
	NNRTIs	Efavirenz, Delavirdine, Nevirapine
	PIs	Amprenavir, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir
	Fusion inhibitors	Enfuvirtide
Other antiviral agents		Adefovir, Fomivirsen, Imiquimod, Inosine,Interferon, Podophyllotoxin, Ribavirin, Viramidine

Category: Antiretroviral drugs

EAST Search History

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